REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, Claims 49-63 were pending in this application and were rejected on various grounds. With this amendment, Claims 59-63 have been cancelled, and Claims 49, 53, and 58 have been amended to clarify what Applicants have always regarded as their invention. All cancellations and amendments were done without prejudice or disclaimer. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications. In the following arguments, the rejections will be addressed in the order they are raised in the Office Action, with reference to the paragraph numbering used in the Office Action.

Correspondence address

A new Power of Attorney was filed in this case on March 23, 2005, and a Notice of Acceptance mailed on April 25, 2005. Accordingly, Applicants respectfully request the Examiner to note the new correspondence address:

Ginger R. Dreger
Heller Ehrman, LLP
275 Middlefield Road,
Menlo Park, CA 94025

Applicants request all future correspondence in this case to be sent to the above mentioned address.

Priority

Re 2: The Examiner asserts that the claims pending in this application are entitled only to the priorities of PCT/US98/24855 filed 11/20/98, US application 09/254,465 filed 3/5/99 and US application 09/953,499 filed 9/14/01. The Examiner, while acknowledging that PCT/US98/19437 filed 9/17/98 also disclosed the amino acid sequence of PRO245 and the encoding nucleotide sequence, holds that "only the three priority applications listed above

disclose an enabled use for PRO245, namely, that it inhibits VEGF stimulated proliferation of endothelial cells or induces apoptosis in endothelial cells." (Page 2 of the instant Office Action).

Applicants rely on the Inhibition of VEGF Stimulated proliferation of endothelial cell growth assay (Example 4, Page 53) for patentable utility which was first disclosed in PCT/US98/24855 filed 11/20/98, priority to which has been claimed in this application. Further, the PRO245 DNA and the amino acid sequence were first disclosed in the PCT/US98/19437 filed 9/17/98, priority to which has been claimed in this application. Accordingly, Applicants respectfully request that 9/17/98 (PCT/US98/19437) be accorded as the earliest priority to Claims 49-63.

Specification

Re 3: As requested by the Examiner, the specification has been amended on Page 1 to reflect the status of parent application Nos. 09/953,499 and 09/254,465.

Re 6: The specification was objected to for allegedly failing to provide a brief description of each individual figure. The legends of Figures 1, 9 and 10 have been amended to refer to Figures 1A and 1B, Figures 9A and 9B, and Figures 10A and 10B, respectively. It was not necessary to amend the description of the figures since the "individual panels" of Figures 1A and 1B, and 9A and 9B show the same sequences, which did not fit one page, and the legend to Figures 10A and 10B already contained a separate description for the two panels.

Re 7: Applicants note that the amendment to the specification on page 68, filed 2/24/04 was found to be sufficient to satisfy the deposit of plasmid DNA35638-1141. In addition, Applicants have not supplemented the original statement by specifically confirming that the deposit was made under conditions specifically assuring the maintenance of a viable culture for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository.

Information Disclosure Statement

Re 4: In acknowledging the consideration of the IDS's filed on 6/7/04 and 4/18/05, the Examiner notes that the BLAST results provided as reference numbers 15-17 are not appropriate for IDS, and requests that at least the Accession No., Database and earliest available date of

reference should be provided. The BLAST results listed as items 15-17 were included in the IDS solely for sake of completeness. Information about the sequences contained in the BLAST results is provided in the rest of the IDS. Therefore, the information is complete, and the deletion of items 15-17 is appropriate.

Sequence Listing and Figures

Re 5: The Examiner found a discrepancy between the sequence set forth in Figure 5 and SEQ ID NO: 11. It has been found that, due to an inadvertent and obvious mistake, SEQ ID NO: 11 is a duplicate of SEQ ID NO: 7, and does not correspond to the sequence of Figure 5. The attached substitute Sequence Listing corrects this mistake. While preparing the corrected Sequence Listing, Applicants have additionally found that Figure 5, as filed with the present application, lacks certain N-terminal nucleotides, which have been covered by the designation "SEQ ID NO: 11." Accordingly, a new Figure 5 is also submitted with the present Amendment and Response, which corrects this error. Since the entire nucleotide sequence of Figure 5 was properly shown in Figure 2 of provisional application 60/066,364, the entire disclosure of which has been incorporated by reference into the present application, the present submission of the correct complete sequence does not constitute new matter.

Claim Rejections – 35 U.S.C. § 112, first & second paragraph

Re 9: Claims 53, 58 and 63 are rejected under 35 USC 112, second paragraph, allegedly "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner further alleges that "The use of "PRO245" polypeptide as the sole means of identifying the claimed polypeptide renders the claim indefinite..."(Page 3 of the Instant Office Action).

Applicants have amended Claims 53, 58-59 and 63 to recite "SEQ ID NO:9" and no longer recite "PRO245." Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Re 11: Claims 49-53 were rejected under 35 USC 112, first paragraph allegedly "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Page 3 of the instant Office

Action) In particular, according to the Examiner, the phrase "having at least 95% sequence identity" in claim 49, line 1, represents a departure from the specification and the claims as originally filed.

Applicants respectfully disagree.

At page 12, lines 24-33, the specification provides the following disclosure:

> "PRO301 variant" or "PRO245 variant" means an active PRO301 as defined below, having at least about 80% amino acid sequence identity to (a) a DNA molecule encoding a PRO301 polypeptide, with or without its native signal sequence, with or without the initiating methionine, with or without the potential transmembrane domain, and with or without the intracellular domain or (b) the complement of the DNA molecule of (a). In a particular embodiment, the PRO301 variant has at least about 80% amino acid sequence homology with the PRO301 having the deduced amino acid sequence shown in Fig. 1 (SEQ ID NO: 1) for a full-length native sequence PRO301. Such PRO301 variants include, for instance, PRO301 polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the sequence of Fig. 2 (SEQ ID NO: 1). Preferably the nucleic acid or amino acid sequence identity is at least about 85%, more preferably at least about 90%, and even more preferably at lest about 95%.

As it is clear from the first line, this section is intended to provide a definition for PRO301 and PRO245 variants, but, due to a typographical error, the rest of the paragraph refers only to PRO301 variants. The first sentence, when ready literally, would indicate that PRO301 variants and PRO245 variants are the same, which is clearly untrue in view of the rest of the specification, where PRO301 and PRO245 are described as having different sequences and activities. In view of this, one of ordinary skill in the art would immediately recognize that the paragraph at page 12, lines 24-33 contains a typographical error, and would also know how to correct that error, by extending the disclosure to PRO245 variants. Accordingly, the cited paragraph provides clear support for PRO245 variants having at least about 95% sequence identity to the sequence of PRO245, and the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Re 12: Claims 49-63 are rejected under 35 USC 112, first paragraph as allegedly "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims"

(Page 4 of the Instant Office Action). The Examiner further alleges "the genus claims encompass "an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. There are no working examples of nucleic acids less than 100% identical to SEQ ID NO:8....The claims are broad.....and have no functional limitation". (Page 5 of the Instant Office Action).

Claims 59-63 have been canceled. The rejection of the remaining claims is respectfully traversed.

The claims, in their broadest aspect, now recite isolated nucleic acid molecules encoding a polypeptide having at least 95% sequence identity to SEQ ID NO: 9, wherein the encoded polypeptide is capable of inhibiting VEGF-stimulated endothelial cell growth.

Methods of making variants of native polypeptides were well known in the art at the effective filing date of the present application. In addition, the specification provides a detailed description of an assay for testing the inhibition of VEGF-stimulated endothelial cell growth. Based on this disclosure, one of ordinary skill in the art at the time the present invention was made would have been able to make and test the claimed variants of the polypeptide of SEQ ID NO: 9 (PRO245) without undue experimentation. Therefore, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Re 13: Claims 49-63 are rejected under 35 U.S.C. §112, first paragraph, allegedly "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention." (Page 6 of the Instant Office Action).

Claims 59-63 have been canceled. The rejection of the remaining claims is respectfully traversed.

The written description requirement serves to satisfy the inventor's obligation to both disclose to the public the invention for which a patent is sought and to demonstrate that the inventor was in the possession of the invention that is claimed. See Enzo Biochem, Inc. v. Gene-Probe, Inc., 296 F.3d 1316, 1330 (Fed. Cir. 2002) (the written description requirement "is the quid pro quo of the patent system; the public must receive meaningful disclosure in exchange

from being excluded from practicing the invention for a limited period of time"); Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345-46 (Fed. Cir. 2000) (the purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification"). The application of this requirement is case specific, and includes consideration of both the state of the art and of the predictability in the relevant art.

Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if: (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity a given limited degree of sequence identity to the sequence actually disclosed and tested, the written description requirement is met. As the invention claimed in claims 49-63 meets these requirements, the present rejection should be withdrawn.

It is well settled that patent Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed (Emphasis added).[1]

The claims, in their broadest aspect, are now directed to nucleic acid molecules comprising a nucleotide sequence encoding a polypeptide having at least a 95% sequence identity to the sequence of SEQ ID NO: 9, wherein such polypeptides are capable of inhibiting VEGF-stimulated endothelial cell growth. It is well settled that written description for a genus can be provided by a combination of structural and functional features, such as it has been done in the present case. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

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[1] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Claim Rejections – 35 U.S.C. §102

Re 16: Claims 59 is rejected under 35 USC 102(b) as allegedly being anticipated by Bonaldo et al Genome Res.6(9):791-806 (1996). Examiner asserts that "Bonaldo et al teach a 753 nucleic acid molecule comprising a nucleic acid that is 100% identical to nucleic acids 1-661 of SEQ ID NO:8," (Pages 7-8 of the Instant Office Action)

The rejection is moot in view of the cancellation of claim 59.

Claim Rejections – 35 U.S.C. §103

Claims 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonaldo et al Genome Res.6(9):791-806 (1996) in view of Darnell et al.

The cancellation of claims 60-63 obviates this rejection.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1216 R1D6**).

Respectfully submitted,

Date: December 4, 2006

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